REMARKS

Applicants respectfully request entry of amendments to claims 1, 16-18, 20, 22, 26, and 32-36. Please cancel claims 3, 4, 12-15, 27-30, and withdraw claims 31 and 37, without prejudice or disclaimer.

Support for the amendments can be found throughout the specification, including the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 1, 2, 5-11, 16-26, 32-36, and 38-42 are in condition for allowance, or are in better condition for presentation on appeal, and respectfully request that the claims as amended be entered.

Priority

The Office Action alleges that the claim for the benefit of priority under 35 U.S.C. §119(e) to Provisional Application No. 60/403,637 (hereinafter, the '637 application) is acknowledged to be August 16, 2003. However, the correct filing date for the '637 application is August 16, 2002. Applicants request that the record be corrected to acknowledge the August 16, 2002 benefit date.

Drawings

The drawings are objected to as allegedly being non-compliant with 37 C.F.R. §1.121(d). While not acquiescing to the reasoning offered in the Office Action, Applicants have provided herewith a corrected Figure 25.

Objections

Applicants have provided herewith corrected claims 1 and 20. For this reason, Applicants respectfully request that the objections be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 1, 2, 5-7, 9, 10, 12-26, 32-36, and 38-40 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Smith et al., Fleming et al., and Fulton et al. As claims 12-15 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 U.S.P.Q.2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The claimed methods comprise administration of a polynucleotide encoding a mutant eNOS polypeptide wherein the eNOS polypeptide comprises at least one mutation at a position that is phosphorylated in wild-type eNOS in mammalian cells, the position being in the calmodulin-binding domain corresponding to amino acid residues 478-522 of SEQ ID NO:1 and wherein the eNOS polypeptide has increased eNOS activity, as compared to a wild-type eNOS polypeptide. Applicants submit that neither Smith et al., Fleming et al. nor Fulton et al., alone or in combination, teach or suggest the use of a polynucleotide encoding a mutant eNOS polypeptide as claimed.

The Office Action admits, in pertinent part, that Smith et al. do not teach a method for treating CLI comprising the administration a mutant mammalian eNOS polypeptide. The Action then provides Fleming et al. and Fulton et al. to cure the deficiency identified in the primary reference. Fleming et al. describe eNOS mutants with an Ala or an Asp substituted for the wild-type Thr at position 495 and demonstrates a difference between the two mutants in sensitivity to activation by Ca^{2+} and calmodulin. However, Fleming et al. do not teach that these mutants have

an increase in eNOS activity compared to wild type eNOS. For example, Ala or Asp substitution at residue 495 required twice the concentration of free Ca^{+2} (i.e., 1.0 μmol/L vs. 0.5 μmol/L; see legend of Figure 9) and 3 times the amount of CaM (i.e., 3 μmol/L vs. 1 μmol/L; gray bars, see legend of Figure 9) to achieve the equivalent activity of wild type eNOS (e.g., compare gray bars in Figure 9A and with Figure 9B). This data suggests that at the same concentration of Ca^{+2} and CaM, the eNOS activity of the mutants would be less than wild type, given the trend of increasing activity with increasing concentration of the two agents (see Figure 9A and 9B). Such data does not support the position that Fleming et al. teach a mutant with increased eNOS activity. Further, because Fulton et al. describe an eNOS with mutation at serine 1177 with an intact calmodulin-binding domain, the combination of the references would not achieve the invention as claimed; i.e., a method of treatment of CLI with a mutant comprising a substitution at residue 495 or substitutions at residues 495 and 1177, where the mutant has increased eNOS activity, as compared to wild-type eNOS polypeptide . Therefore, one of skill in the art would not be motivated to combine such teachings.

Thus, because the teachings of Smith et al. would not result in the invention as claimed when combined with the teachings of Fleming et al. and Fulton et al., one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings.

It is axiomatic that one cannot simply use the Applicants' disclosure as a "blueprint" to reconstruct, by hindsight, Applicants, claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). As there is neither the suggestion nor expectation of success that can be found in the cited art, no *prima facie* case of obviousness exists.

In sum, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 1, 9, 35-36, 38, 40, and 42 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Smith et al., Fleming et al., as applied to claims 1, 2, 5-7, 9, 10, 12-26, 32-36, and 38-40, and in further view of Alberts et al. As claims 12-15 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 U.S.P.Q.2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The claimed methods comprise administration of a polynucleotide encoding a mutant eNOS polypeptide wherein the eNOS polypeptide comprises at least one mutation at a position that is phosphorylated in wild-type eNOS in mammalian cells, the position being in the calmodulin-binding domain corresponding to amino acid residues 478-522 of SEQ ID NO:1 and wherein the eNOS polypeptide has increased eNOS activity, as compared to a wild-type eNOS polypeptide. Applicants submit that neither Smith et al., Fleming et al. nor Alberts et al., alone or in combination, teach or suggest the use of a polynucleotide encoding a mutant eNOS polypeptide as claimed.

The Office Action admits, in pertinent part, that Smith et al. do not teach a method for treating CLI comprising the administration a mutant mammalian eNOS polypeptide. The Action then provides Fleming et al. and Alberts et al. to cure the deficiency identified in the primary reference. Fleming et al. describe eNOS mutants with an Ala or an Asp substituted for the wild-type Thr at position 495 and demonstrates a difference between the two mutants in sensitivity to activation by Ca^{2+} and calmodulin. However, Fleming et al. do not teach that these mutants have an increase in eNOS activity compared to wild type eNOS. For example, Ala or Asp substitution

at residue 495 required twice the concentration of free Ca^{+2} (i.e., 1.0 μmol/L vs. 0.5 μmol/L; see legend of Figure 9) and 3 times the amount of CaM (i.e., 3 μmol/L vs. 1 μmol/L; gray bars, see legend of Figure 9) to achieve the equivalent activity of wild type eNOS (e.g., compare gray bars in Figure 9A and with Figure 9B). This data suggests that at the same concentration of Ca^{+2} and CaM, the eNOS activity of the mutants would be less than wild type, given the trend of increasing activity with increasing concentration of the two agents (see Figure 9A and 9B). Such data does not support the position that Fleming et al. teach a mutant with increased eNOS activity. Further, while Alberts et al. is provided to suggest that Ala, Val, Leu, and Ile would be conservative substitutions, the combination of the references would not achieve the invention as claimed. Therefore, one of skill in the art would not be motivated to combine such teachings.

Thus, because the teachings of Smith et al. would not result in the invention as claimed when combined with the teachings of Fleming et al. and Alberts et al., one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings.

It is axiomatic that one cannot simply use the Applicants' disclosure as a "blueprint" to reconstruct, by hindsight, Applicants' claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). As there is neither the suggestion nor expectation of success that can be found in the cited art, no *prima facie* case of obviousness exists.

In sum, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 1, 8-11, 35, 36, 41, and 42 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Smith et al., Fleming et al., and Alberts et al. as applied to claims 1, 2, 5-7, 9, 10, 12-26, 32-36, 38-40, and 42, and in further view of Liu et al. As claims 12-15 have been canceled, the rejection as applied to these claims is rendered moot.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 U.S.P.Q.2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The claimed methods comprise administration of a polynucleotide encoding a mutant eNOS polypeptide wherein the eNOS polypeptide comprises at least one mutation at a position that is phosphorylated in wild-type eNOS in mammalian cells, the position being in the calmodulin-binding domain corresponding to amino acid residues 478-522 of SEQ ID NO:1 and wherein the eNOS polypeptide has increased eNOS activity, as compared to a wild-type eNOS polypeptide. Applicants submit that neither Smith et al., Fleming et al., Alberts et al., nor Liu et al., alone or in combination, teach or suggest the use of a polynucleotide encoding a mutant eNOS polypeptide as claimed.

The Office Action admits, in pertinent part, that Smith et al. do not teach a method for treating CLI comprising the administration a mutant mammalian eNOS polypeptide. The Action then provides Fleming et al., Alberts et alt., and Liu et al. to cure the deficiency identified in the primary reference. Fleming et al. describe eNOS mutants with an Ala or an Asp substituted for the wild-type Thr at position 495 and demonstrates a difference between the two mutants in sensitivity to activation by Ca^{2+} and calmodulin. However, Fleming et al. do not teach that these mutants have an increase in eNOS activity compared to wild type eNOS. For example, Ala or

Asp substitution at residue 495 required twice the concentration of free Ca^{+2} (i.e., 1.0 μmol/L vs. 0.5 μmol/L; see legend of Figure 9) and 3 times the amount of CaM (i.e., 3 μmol/L vs. 1 μmol/L; gray bars, see legend of Figure 9) to achieve the equivalent activity of wild type eNOS (e.g., compare gray bars in Figure 9A and with Figure 9B). This data suggests that at the same concentration of Ca^{+2} and CaM, the eNOS activity of the mutants would be less than wild type, given the trend of increasing activity with increasing concentration of the two agents (see Figure 9A and 9B). Such data does not support the position that Fleming et al. teach a mutant with increased eNOS activity. Further, this deficiency is not cured by Alberts et al. or Liu et al. Therefore, one of skill in the art would not be motivated to combine such teachings.

Thus, because the teachings of Smith et al. would not result in the invention as claimed when combined with the teachings of Fleming et al. Alberts et al. and Lui et al., one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings.

It is axiomatic that one cannot simply use the Applicants' disclosure as a "blueprint" to reconstruct, by hindsight, Applicants' claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). As there is neither the suggestion nor expectation of success that can be found in the cited art, no *prima facie* case of obviousness exists.

In sum, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

Conclusion

Applicants submit that pending claims 1, 2, 5-11, 16-26, 32-36, and 38-42 are in condition for allowance, or are in better condition for appeal. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

Please charge Deposit Account 07-1896 in the amount of $525.00 for a Three-Month Extension of Time. The Commissioner is hereby authorized to charge any additional fees required by this submission, or make any credits or overpayments, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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